



NATIONAL INSTITUTES OF HEALTH

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IN REPLYING ADDRESS THE
NATIONAL INSTITUTE OF MENTAL HEALTH
ADDICTION RESEARCH CENTER
U.S. PUBLIC HEALTH SERVICE HOSPITAL
P. O. Box 2000
LEXINGTON, KENTUCKY

~~HAAK~~ ~~SWB~~
~~S-D~~ ~~SS.~~
~~CHAD~~ ~~WED~~
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m

(b)(3)

On checking I find that I have only 50 mg. of the drug MK-57. Chemically this compound is 6-methyl- Δ -6-desoxymorphine. I am writing Merck and Company to see if I can obtain an additional supply.

Megimide is being shipped under separate cover.

I am enclosing three reprints on suggestibility by V. H. Vogel.

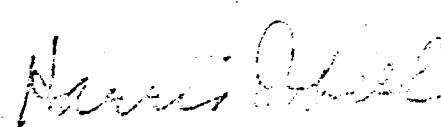
I am also enclosing tables of the preliminary tabulations on C-9 and MX. These experiments were preceded by preliminary titration in which it was determined that 0.6 to 1.0 mg. of MX for each 70 kilograms of bodyweight induced definite cardiovascular changes. Thereafter, a comparison was carried out in 15 subjects, using the randomized Latin Square design. The drugs tested were placebo; 0.6 mg MX (per 70 kilos); 1 mg MX (per 70 kilos); and 1 mg. C-9 (per 70 kilos). Measurements including reclining pulse rate (after 10 minutes in bed); standing pulse rate (counted for one minute after standing for one minute); and number of positive responses to a simple system check-list based on our earlier work with C-9.

Two tables are enclosed. One shows the time course of the effect with different drugs. In this table it is evident that the effect does not begin until the second hour and persists at least until the twelfth hour.

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c-760

The second table shows the average changes with the four different combinations. You will notice that there is a distinct difference between both doses of MX and placebo, as well as between C-9 and placebo. There is also a definite dose response between the 0.6- and 1.0-mg. level with MX. There may be a tendency for cardiovascular effects of C-9 to be more pronounced in the overall course. I cannot be certain of this until the statistical analysis has been completed. When this is accomplished I will send you another report and will also work up table showing the details on the cardiovascular measurements made in the older work with C-9.

Sincerely yours,


Harris Isbell, M.D.
Director

HI:rn

Enclosures: 5

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TIME COURSE OF C-9 EFFECTS

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ASUS ¹	DRUG ¹	HOUR BEFORE OR AFTER DRUG													
		-1	+1	+2	+3	+4	+5	+6	+7	+8	+9	+10	+11	+12	+13
CLINICAL TEST	Placebo Mix 0.6 Mix 1.0 C-9 1.0	61	66	64	63	63	67	70	65	66	64	71	67	64	62
		61	65	66	67	66	70	72	69	67	68	73	73	65	63
		62	66	70	72	69	74	75	73	72	71	74	72	69	61
		61	66	75	73	69	71	78	74	74	74	77	72	68	65
STANDING TEST	Placebo Mix 0.6 Mix 1.0 C-9 1.0	90	85	91	89	85	89	93	92	91	84	80	86	89	89
		86	85	93	98	93	97	102	100	97	93	97	95	87	92
		90	88	106	106	107	106	110	109	106	97	100	99	92	95
		90	86	102	110	111	107	112	113	114	105	109	92	91	97
ESTIMATES	Placebo Mix 0.6 Mix 1.0 C-9 1.0	0	0	1	1	2	2	2	1	1	1	1	1	1	0
		0	0	2	2	3	3	4	4	4	3	3	2	3	0
		0	0	2	3	4	5	5	5	5	5	5	4	4	1
		0	0	2	3	4	4	6	5	5	5	4	4	3	0

Doses expressed as mg/70 kg (e.g. 1.0 = 1.0 mg for each 70 kg body weight).

Counted for 1 minute after standing quietly for 1 minute.

AVERAGE CHANGES $\pm$ STANDARD ERRORS AFTER C-9 AND MX IN 15 SUBJECTS

MEASURE	PLACEBO	MX 0.6 ^x	MX 1.0	C-9 1.0
RECLINING ¹ PULSE RATE	590 $\pm$ 12	611 $\pm$ 11	642 $\pm$ 16	654 $\pm$ 22
STANDING ² PULSE RATE	804 $\pm$ 16	859 $\pm$ 20	927 $\pm$ 13	945 $\pm$ 31
QUESTIONS ³	13 $\pm$ 7	33 $\pm$ 11	46 $\pm$ 18	45 $\pm$ 10

¹ Represents sum of rates obtained at one to nine hours after drug.

² Counted for one minute after standing one minute. Represents average sum of rates obtained at one to nine hours after drug.

³ Represents total of positive responses in 23 hours.

^x Dose in mg. for each 70 kg. of body weight.

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